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Similarity trials

A European guideline on biosimilar monoclonal antibodies suggests smaller trials with homogeneous, younger patient groups may suffice for marketing authorization.

The European regulatory authorities continue to make strides forward with biosimilars. Indeed, the latest advice from the European Medicines Agency (EMA) to those seeking to produce biosimilar monoclonal antibodies (mAbs) is really quite straightforward. In its draft *Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies* released for consultation in November, the Committee for Medicinal Products for Human Use (CHMP) of the EMA, in essence, said two things. First, applicants seeking approval of biosimilar mAbs will have to undertake comparative clinical studies; they must show that the safety and efficacy performance of a biosimilar is indeed similar to that of a reference, originator compound. But, second, clinical work doesn't have to be too onerous, especially if applicants are smart about the way they choose the patient population. This latter point has received remarkably little attention but could be pivotal in shaping the biosimilars marketplace as the cost and complexity of running trials is the biggest barrier to market entry by generics companies.

The expensive part of the process of developing biosimilars was always going to be the clinical work. But the overarching guidelines that the CHMP published on biosimilars (not specifically mAbs) in 2005 were rather vague on the nature of those trials. Indeed, the guidelines barely deserved the name, so little guidance did they actually give, and so few lines did they draw. The 2005 CHMP documentation did little more than identify who companies needed to talk to at EMA when taking their product forward on, in essence, a case-by-case basis.

The 2010 antibody guidelines are much more specific. The key passages in the document still steer applicants firmly toward upfront discussion with the European regulator, which might be construed as a return to a case-by-case system. But the document also plants several highly significant signposts, all of which point in the same direction—that of simpler, smaller clinical studies.

The focus of the biosimilarity exercise, says the guideline, is to "demonstrate similar safety and efficacy compared to the reference product, not patient benefit *per se*." So the idea is not to reproduce the trial for the original approval, but to design a trial that shows the compounds are similar.

How would such a trial be done? Well the guideline has sage advice there, too.

First, choose a sensitive, experimental human model. In other words, select a clinical population where, from knowledge of the reference biologic, you would expect the drug to make a big impact. In that way, the similarity trial would be comparing one big impact with (one hopes) a second, similarly big impact. Comparing two large impacts would enable any differences to be more apparent.

Second, the guideline suggests using homogeneous patient populations. By taking variability out of the patient set, any variability between the brand and the biosimilar forms of the biologic would be more apparent, the CHMP argues. The guideline also points out that with a homogeneous population, the sample size needed to prove (or disprove) equivalence would be smaller and facilitate simpler interpretation. It warns against using patients who either have different disease severity or have been exposed to different prior treatments because these additional variables could complicate the interpretation of differences seen in the two drug arms of the study. The guideline even recommends using younger groups of patients where possible, because younger people would be less likely to be effected by "concomitant clinical conditions."

In short, a trial to establish similarity is quite unlike a trial designed to measure safety and efficacy.

Thus, with its new guideline on biosimilar mAbs, the EMA has not only provided specific and lucid advice to industry but, importantly, kept the debate about biosimilars and brands on a firm and rational footing. The US situation, in contrast, remains rather different.

The 2010 Patient Protection and Affordable Care Act passed last March contained a section providing a legal framework for the approval of follow-on biologics. At the beginning of November, the US Food and Drug Administration held a two-day hearing in Silver Spring, Maryland, to discuss some of the issues with different stakeholders.

Understandably perhaps for a first meeting, much of the debate was polarized between generics firms, which called for low clinical hurdles to biosimilarity, and innovator companies, which called for high ones. There were polemics over whether a biosimilar approved in more than one indication would require comparative trials in each of those indications. There were distracting discussions on a phenomenon known as drift, wherein the manufacturing processes for a biologic and its biosimilar evolve away from each other. There were debates on whether trials should establish noninferiority or equivalence. And the possibility was discussed that a thorough analysis of post-translational modifications, three-dimensional structure and protein aggregation might obviate the need for clinical work altogether. That seems extraordinarily unlikely given the current state of technology and experience gained so far.

It is striking how far behind Europe the US regulatory pathway for follow-on biologics remains. Part of this is due to the weaker political impetus and greater lobbying strength of US-based innovator companies. But governmental momentum to push forward might change if it became evident that healthcare costs could be substantially reduced by means of follow-on products for expensive biologics and mAbs. If, as EMA suggests, abbreviated trials with homogeneous patient groups are sufficient to support a marketing authorization of a biosimilar, many more generics companies are likely to enter the biosimilars/follow-on market, increasing price competition and driving down healthcare costs.

Thus far, clinical trials for biosimilars in Europe haven't looked much smaller or less costly than those required for applying for a new marketing authorization. But the guideline on biosimilar mAbs provides the first tantalizing indication that smaller trials may indeed be possible.